

Serum Plant Sterols and Atherosclerosis: Is There a Place for Statin-Ezetimibe Combination?

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We read with interest the paper by Miettinen et al. (1) demonstrating that the higher the absorption of cholesterol, the higher the plant sterol contents are in serum resulting in their higher contents in atherosclerotic plaque. The prospective Cardiovascular Munster (PROCAM) study found that people in the upper quartile of sitosterol levels had a 1.8-fold increased risk of major coronary events compared with those in the lower three quartiles (2). Statin treatment decreases cholesterol synthesis but increases absorption of plant sterols (3). In the Scandinavian Simvastatin Survival Study (4S), no reduction was observed in recurrence of coronary heart disease with the use of simvastatin in patients with high baseline plant sterol contents and with marked increase of serum plant sterols during the five-year treatment period (4). Additional treatment with inhibition of sterol absorption (e.g., with plant stanol esters) was suggested for this particular group of patients (3,4). To this respect, we were surprised that Miettinen et al. (1) did not consider the potential of combining ezetimibe with statin. Indeed, in addition to inhibiting intestinal cholesterol absorption, a well-known effect, ezetimibe also reduces plasma concentrations of the non-cholesterol sterols sitosterol and campesterol, suggesting an effect on the absorption of these compounds as well (5). It has been demonstrated recently that the Niemann-Pick C1-like 1 (NPC1L1) transporter is most likely responsible for the transport of cholesterol and plant sterols from the brush border membrane into the intestinal mucosa (6). The intestinal absorption of plant sterols differs markedly from that of cholesterol and their biliary excretion as well. The presence of two specific ABCG5/ABCG8 transporters in the intestinal wall is responsible for rapid resecretion of plant sterols into the intestine lumen and thus rather low intestinal absorption of campesterol and sitosterol, and their presence in the liver explains why plant sterols are excreted much faster in the bile than cholesterol (7,8). Ezetimibe interferes with NPC1L1, reducing the intestinal uptake of cholesterol and plant sterols (6-8). Interestingly, the reduction of plant sterol serum levels with ezetimibe was significantly more pronounced than the reduction of serum cholesterol (7,8). Clinical data on ezetimibe could demonstrate that the concept of inhibiting intestinal absorption of neutral sterols is beneficial in both patients with hypercholesterolemia as well in patients with hypersitosterolemia, an inherited disease with identified mutations in ABCG5/ABCG8 transporters that leads to a high prevalence of cardiovascular disease (9). Recent observations, such as those by Miettinen et al. (1), that elevated serum plant sterols pose an increased cardiovascular risk suggest that increases of serum plant sterol levels should be avoided, especially in atherosclerosis-prone individuals (1). Therefore, subjects with high cholesterol absorption and low synthesis may need a therapy combining statin and ezetimibe to lower more effectively their serum cholesterol levels and prevent an increase in the levels of plant sterols (3). The question remains, however, as to whether lowering serum levels of plant sterols (especially in high-absorber patients on statin therapy) with a drug such as ezetimibe will decrease the incidence of coronary artery disease.

REFERENCES

1. Miettinen TA, Railo M, Lepäntalo M, Gylling H. Plant sterols in serum and in atherosclerotic plaques of patients undergoing carotid endarterectomy. *J Am Coll Cardiol* 2005;45:1794-801.
2. Assmann G, Cullen P, Erbey JR, et al. Elevation in plasma sitosterol concentration is associated with an increased risk for coronary events in the PROCAM study (abstr). *Circulation* 2003;108:IV730.
3. Miettinen TA, Strandberg TE, Gylling H, for the Finnish Investigators of the Scandinavian Simvastatin Survival Study Group. Noncholesterol sterols and cholesterol lowering by long-term simvastatin treatment in coronary patients. Relation to basal serum cholesterol. *Arterioscler Thromb Vasc Biol* 2000;20:1340-6.
4. Miettinen TA, Gylling H, Strandberg T, Sarna S, for the Finnish 4S Investigators. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. *BMJ* 1998;316:1127-30.

5. Sudhop T, Lütjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106: 1943-8.
6. Davis HR, Zhu LJ, Hoos LM, et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole body cholesterol homeostasis. *J Biol Chem* 2004;279:33586-92.
7. von Bergmann K, Sudhop T, Lütjohann D. Cholesterol and plant sterol absorption: recent insights. *Am J Cardiol* 2005;96 Supp:10D-4D.
8. Sudhop T, Lütjohann D, von Bergmann K. Sterol transporters: targets of natural sterols and new lipid lowering drugs. *Pharmacol Ther* 2005;105:333-41.
9. Salen G, von Bergmann K, Lütjohann D, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004;109:966-71.

REPLY

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In the letter by Drs. Radermecker and Scheen, it was noted that we have not commented the potential of combining ezetimibe to statins (1). The additional low-density lipoprotein (LDL) lowering of combining cholesterol absorption inhibitors to statins is relatively small, usually approximately 15%, for instance, for ezetimibe or plant stanols. No clinical studies have been published defining their additional reduction of coronary events during these treatments, which seems to be true also for their monotherapy, even though they are suitable for treatment of modestly increased LDL cholesterol, and stanol ester management also provides the heart-healthy fatty acids. Relatively low LDL cholesterol lowering either in mono- or in combination with statin treatment certainly requires randomized large-enough study populations treated for relatively long periods of time to record changes in heart events. In addition to LDL cholesterol lowering, cholesterol absorption inhibitors lower also plant sterol levels off or on statin treatment. Thus, they also normalize statin-induced increase of plant sterols. The endarterectomized patients treated with statin in our study had increased serum plant sterol ratios to cholesterol, which appeared also to be reflected in atheromatous plaques of carotid arteries (1). This finding certainly rises a question as to whether the lowering of serum plant sterols with cholesterol absorption inhibitors, e.g., ezetimibe or plant stanols, also could reduce plant sterol contents in the plaques. However, it also raises the question of whether an increase of serum plant sterols, e.g., during the consumption of plant sterol-enriched functional foods, also could enhance their concentrations in atheromatous plaques. Several studies have shown that increased serum plant sterols, even their ratios to cholesterol, are associated with enhanced coronary artery disease in crossover or follow-up investigations (2). However, in the Scandinavian Simvastatin Survival Study, no association was found in the control group between the five-year coronary events and baseline plant sterol concentrations or ratios to cholesterol (2). In the respective simvastatin treatment group, coronary events were reduced significantly in the low absorber but unchanged in the high absorbers, suggesting that additional lowering of LDL cholesterol is needed in the latter type of patients, e.g., by combination with cholesterol malabsorption. Statin treatment seems to improve endothelial function of carotid arteries despite increasing serum plant sterols (3); however, vascular function was unaffected with phytosterol-enriched food when LDL cholesterol was lowered and serum plant sterols were increased (4,5). Drs. Radermecker and Scheen concluded that "elevated serum plant sterols pose an increased cardiovascular risk," but clinical heart event reduction with their pharmacological lowering is still open.